AOBIOme

CLINICAL TRIAL PROTOCOL
Phase II

COMPOUND:
B244

A Prospective, Vehicle Controlled, Double Blinded, Multicenter, Randomized, Phase II Study of B244 delivered as a topical spray to Determine Safety and Efficacy in Subjects with elevated blood pressure

STUDY NUMBER: AVB244-003

VERSION DATE: November 30, 2016

Sponsor:
AOBiome LLC

One Broadway

14th Floor

Cambridge, MA 02142-1100

Revision Chronology

Original	July 18, 2016
Amendment 1	September 29, 2016
Amendment 2	October 25, 2016
Amendment 3	November 30, 2016

SPONSOR APPROVAL

A Prospective, Vehicle Controlled, Double Blinded, Multicenter, Randomized, Phase II Study of B244 delivered as a topical spray to Determine Safety and Efficacy in Subjects with elevated blood pressure

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INVESTIGATOR AGREEMENT

I have read this protocol and agree:

- To conduct the study as outlined herein, in accordance with Good Clinical Practices (GCPs), the Declaration of Helsinki and complying with the obligations and requirements of Clinical Investigators and all other requirements listed in 21 CFR part 312 and according to the study procedures provided by AOBiome LLC and local regulations.
- Not to implement any changes to the protocol without prior agreement from the Sponsor and prior review and written approval from the IRB or IEC, except as would be necessary to eliminate an immediate hazard to study participant (s), or for administrative aspects of the study.
- To ensure that all persons assisting me with the study are adequately informed about the investigational product(s) and of their study-related duties as described in the protocol.
- To completely inform all participants in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with GCP and regulatory authority requirements.
- To be responsible for maintaining each participant's consent form in a secure study file and providing each participant with a signed copy of the consent form.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, and any additional information provided to me by, or on behalf of AOBiome LLC.

Investigator Printed Name:_____

Signature:_____ **Date:** _____

Statement of Compliance

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH E6; 62 Federal Register 25691 (1997)

All key personnel (all individuals responsible for the design and conduct of this study) have completed Good Clinical Practice Training.

CLINICAL TRIAL SUMMARY

COMPOUND: B244 STUDY NUMBER: **AVB244-003**

TITLE:	A Prospective, Vehicle Controlled, Double Blinded, Multicenter, Randomized, Phase II Study of B244 delivered as a topical spray to Determine Safety and Efficacy in Subjects with elevated blood pressure
INVESTIGATIONAL PRODUCT	B244
STUDY ARMS	1. B244 applied to the face 2. B244 applied to face and torso
PURPOSE:	**Purpose:** • To evaluate and compare the efficacy of B244 in treating patients with high blood pressure
PRIMARY OBJECTIVES:	• To evaluate the safety and tolerability of B244 in participants with pre- and Stage I hypertension • To assess the efficacy of B244 versus vehicle in reducing in clinic systolic blood pressure in participants with pre- and Stage I hypertension
STUDY DESIGN:	This is a Prospective, Vehicle Controlled, Double Blinded, Multicenter, Randomized Phase II trial, comparing the effect of twice daily B244 application for 4 weeks vs vehicle application on BP and

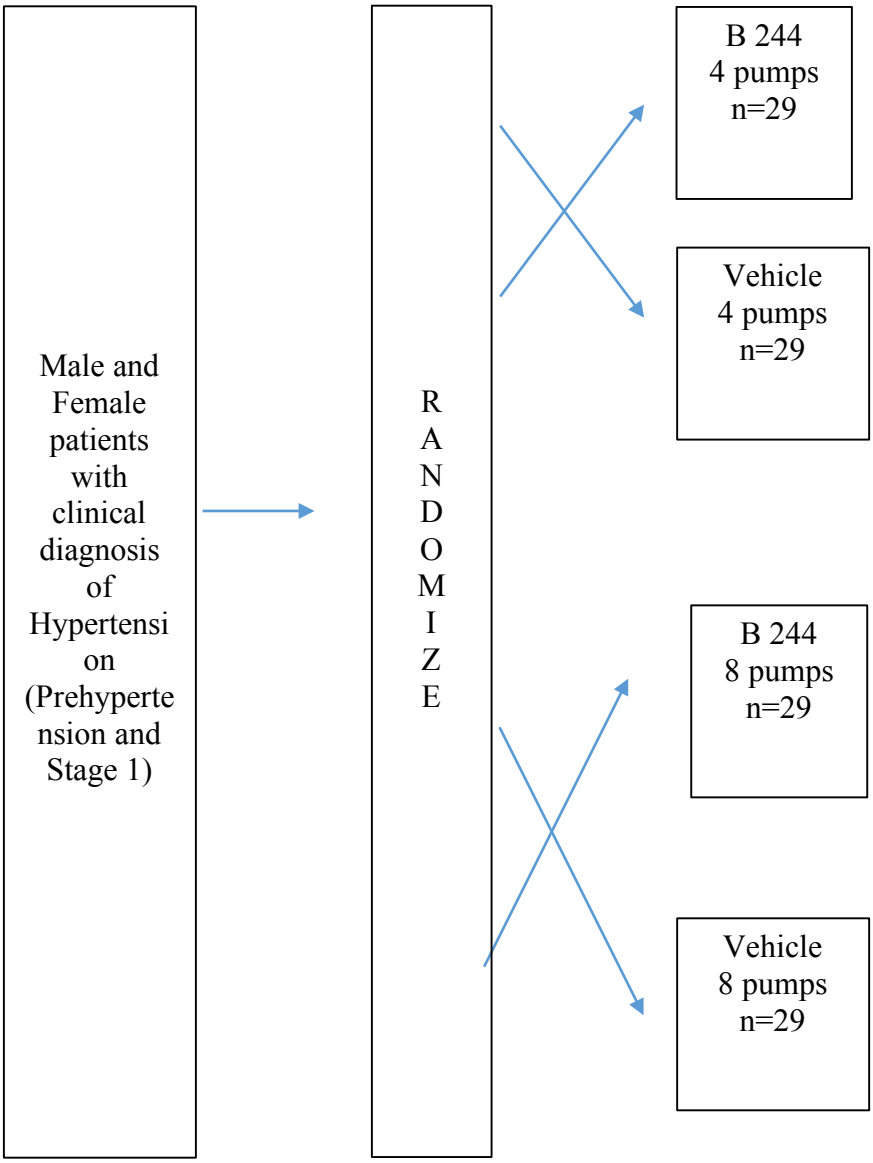
	inflammatory biomarkers. We plan to enroll 116 total patients. Assuming 10% drop out rate, we will plan to complete 104 patients. Randomization will be 1:1 so that equal number of patients will be treated in each Arm of the study. All B244 randomized subjects will be treated at the dose of $8x10^9$ cfu/ml (high-dose of the Phase 1b/2a safety trial)
STUDY POPULATION:	Patients who have clinically confirmed diagnosis of systolic pre hypertension and Stage 1 systolic hypertension are eligible for enrollment. Patients must be in general good health as determined by a thorough medical analysis. Patients must be willing to refrain from using any treatments, investigational products, including herbal medicines for treatment of BP while participating in this study.
MAIN INCLUSION/EXCLUSION CRITERIA:	Inclusion: Participants eligible for enrollment in the study must meet all the following criteria: • Male and female subjects ≥18 years of age • In good general health as determined by a thorough medical history and physical examination, and vital signs • Clinical diagnosis of elevated Blood Pressure defined as: o Having systolic prehypertension measurements having systolic BP (mmHg) of 120-139 and Diastolic BP (mmHg) of ≤90

	○ OR ○ Having Stage 1 systolic hypertension measurements having systolic BP (mmHg) of 140-159 and Diastolic BP (mmHg) of ≤100 • Hypertension treatment naïve patients, defined as those patients who have never been treated with antihypertensive medications or have been off any hypertensive treatment for a period of 12 weeks or longer. • Willing to refrain from using any antihypertensive treatments, other than the investigational product, including herbal supplements, systemic use of steroids, chronic use of NSAIDS, any antihypertensive agents, such as beta-blockers, diuretics, ACE inhibitors, CA channel blockers, Alpha blockers, Central Acting agents and vasodilators. • Ability to comprehend and comply with procedures • Agree to commit to participate in the current protocol • Provide written informed consent prior to any study procedure being performed (all subjects should be able to understand the informed consent form and any other documents that subjects are required to read)
Main Exclusion Criteria:	Participants will be excluded from the study if any of the following criteria are met: • Pregnant and/or lactating women • Patients on treatment for Benign Prostatic Hyperplasia (BPH)

	• Clinically significant history of cardiovascular disease (i. e. PCI, CABG MI (if event occurred ≤ 12 months), atrial fibrillation, frequent PAC, cardiac rhythm disorder, syncope, valve repair/replacement, heart transplantation, PTA, peripheral bypass surgery, endarterectomy, unstable angina, TIA, stroke and NYHF category II, II and IV heart failure. • Patients with renal failure, significant kidney or renal disease defined as having creatinine level of ≥ 1.4 mg/dL • Presence of any condition (medical, psychological, social, or geographical), actual or anticipated, that the Investigator feels would restrict or limit the patient's successful participation for the duration of the study • History of migraines and/or anxiety, where patient is unable to refrain from the use of beta blockers • History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation. • The participant has been previously randomized in this study • Subjects with clinical diagnosis of Type I Diabetes • Subjects with arm circumference of ≥42 cm • Any condition that would prevent the subject from participating in the trial in the opinion of the evaluation

	physician • The participant has received an investigational product within 30 days prior to randomization • Prior use of any product containing B244 or Nitrosomonas eutropha • Unable to lie flat or sit for 15 minutes • Concurrent participation in other trials
DOSE REGIMEN:	After screening and recruitment, participants will be randomized to active or vehicle investigational product (IP) application for 28-days (+/-4 days) . Subjects will apply the spray as follows: • 4 pumps to the Face • 4 pumps to the Face and 4 pumps to the Torso
ASSESSMENT SCHEDULE:	Study assessments will occur on Day 1, weeks 1, 2, 3,4.and 6
STATISTICAL CONSIDERATIONS:	• Intent to treat analysis
INVESTIGATIONAL DRUG AND VEHICLE:	Investigational drug refers to B244. Investigational Product/treatment refers to either B244 or vehicle.
PLANNED DURATION PER SUBJECT:	Up to 8 weeks
DURATION OF STUDY:	First patient in: November 2016 Database Lock: June 2017 The estimated study duration is 12 months. All subjects will be followed from randomization and until their study completion.

1 STUDY SCHEMA



N=116 subjects

2 STUDY FLOW

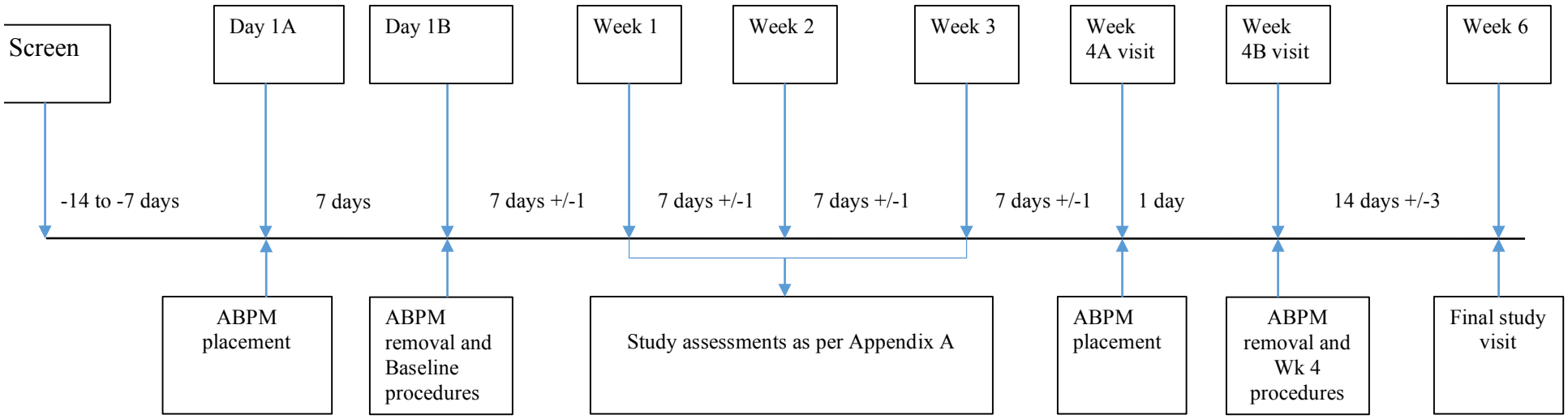

Screen
Day 1A
Day 1B
Week 1
Week 2
Week 3
Week 4A visit
Week 4B visit
Week 6
-14 to -7 days
7 days
7 days +/-1
7 days +/-1
7 days +/-1
7 days +/-1
1 day
14 days +/-3
ABPM placement
ABPM removal and Baseline procedures
Study assessments as per Appendix A
ABPM placement
ABPM removal and Wk 4 procedures
Final study visit

Table of Contents

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

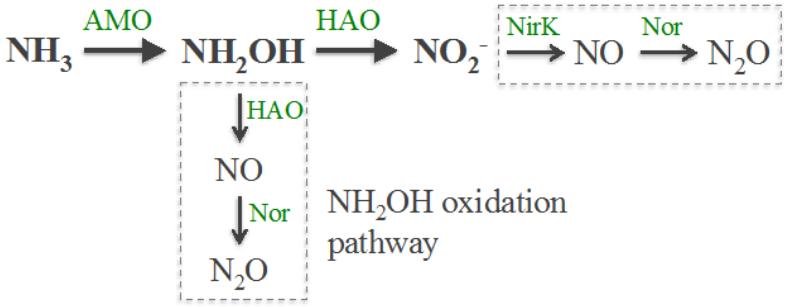
AE	Adverse Event
AMO	Ammonia Monooxygenase
AOB	Ammonia Oxidizing Bacteria
BID	Twice-Daily
CRF	Case Report Form
E/T	Early Termination
FDA	Food and Drug Administration
HAO	NH_2OH oxidoreductase
HbsAg	Hepatitis B Virus Surface Antigen
HCV Ab	Hepatitis C Virus Antibody
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
IP	Investigational Product
IRB	Institutional Review Board
NH_2OH	Hydroxylamine
NH_3	Ammonia
NO	Nitric oxide
NO_2-	Nitrite
SAE	Serious Adverse Event
SPM	Study Procedures Manual

3 INTRODUCTION

3.1 Background

Ammonia oxidizing bacteria (AOB) are essential for the initial step in environmental nitrification processes, specifically the oxidation of ammonia (NH_3) to nitrite (NO_2-). *Nitrosomonas* are Gram-negative chemolithoautotrophic betaproteobacteria that obtain energy solely from NH_3 oxidation, while fixing CO_2 for their carbon needs.[1] Oxidation of NH_3 proceeds in two steps (Figure 1) leading to sequential generation of hydroxylamine (NH_2OH) and NO_2- that require two enzyme complexes: the membrane-bound ammonia monooxygenase (AMO) comprised of subunits AmoA, AmoB and AmoC; and the periplasmic NH_2OH oxidoreductase (HAO). In addition to high NO_2- levels, NH_3 oxidation leads to nitric oxide (NO) and N_2O production through two independent pathways downstream of NH_2OH production: nitrifier denitrification and NH_2OH oxidation.[2]

Figure 1 Nitrifier Denitrification Pathway



B244 is a purified a strain of *Nitrosomonas eutropha* originally isolated from soil samples. Sequencing of the B244 genome revealed a distinct genetic profile from that of other published *Nitrosomonas* strains and AOB genomes. Based on *in vitro* co-culture studies, B244 was able to reduce survival of pathogenic bacteria. Nitrite generation from ammonia concurrently with medium acidification by B244 led to strong antibacterial effects and a marked reduction (~100-fold) in viable counts of methicillin-resistant *Staphylcoccus aureus* and *Pseudomonas aeruginosa*, two pathogens frequently isolated from infected skin and wound sites. In contrast, control cultures with B244 in the absence of ammonium or with heat-killed B244 supplemented with ammonium, had no antibacterial effects. The unique metabolic and antimicrobial activity of *Nitrosomonas*, in combination with their lack of virulence render these bacteria as attractive candidates for topical delivery of nitrite and nitric oxide on human skin with potential to improve health in both normal and abnormal skin conditions or wound sites. NO-releasing drugs or NO donors have also shown activity against *Propionibacterium acnes* and other pathogenic bacteria, anti-inflammatory activity, and inhibition of lipogenesis by insulin-stimulated immortal sebocytes.[4,5]

B244 has been developed as a topical application of a natural source of AOB and NO/NO_x to the human skin. The active ingredient in B244 is available to consumers as a cosmetic product.

Hypertension is one of the most common conditions seen in primary care. About 29% or 1 in 3 American adults have blood pressure[1]. It increases the risk of stroke, heart and kidney disease and is one of the leading causes of death in the US. However, less than 52% of the affected population control their blood pressure[2]. There exists a myriad of combinations to control blood pressure and even though antihypertensive medications can reduce blood pressure immediately,

their prescription would require making over 25 million Americans become patients. Thus, there exists a need to find a medication with little side effect profile that would not only control but potentially prevent hypertension.

B244 is being developed under IND #16487 as a 'live topical' to provide a natural source of AOB and NO/NO_x to the human skin.

To date, two cosmetic studies have been completed of a lower concentration formulation of the active ingredient in B244. In the cosmetic studies, a total of 24 participants applied the cosmetic product to the scalp and 83 participants applied the product to their face. In these studies, there were no reports of drug-related serious adverse events (SAEs).

Under IND #16487, a phase 1b/2a clinical trial was recently completed where 36 participants with clinical diagnosis of facial acne vulgaris were randomized to receive ascending doses of investigational product (IP) over 14 days. Safety analyses have been completed and there have been no attributable drug related SAEs reported.

Blood pressure was measured at screening and Day 1/pre-dose (defined as baseline), during the treatment phase (Day 3, 7, 10, 15) and after 2-week washout on Day 28. For the pooled active dose groups treatment phase systolic blood pressure was reduced by 2.9 mmHg versus baseline (p=0.027) and treatment phase diastolic blood pressure was reduced by 2.4 mmHg versus baseline (p=0.020). In the high dose group ($8x10^9$ cfu/ml), treatment phase systolic blood pressure was reduced by 6.1 mmHg versus baseline (p=0.014) and treatment phase diastolic blood pressure was reduced by 3.5 mmHg versus baseline (p=0.041).

The purpose of this study is to evaluate and compare the efficacy of B244 in treating patients with hypertension.

4 STUDY OBJECTIVES

4.1 Primary Objectives

- To evaluate the safety and tolerability of B244 in participants with pre- and Stage I hypertension
- To assess the efficacy of B244 versus vehicle in reducing in clinic systolic blood pressure in participants with pre- and Stage I hypertension

4.2 Secondary Objectives

- To assess the efficacy of B244 versus vehicle in reducing in clinic diastolic blood pressure in participants with pre- and Stage I hypertension
- To assess the efficacy of B244 versus vehicle in reducing mean ambulatory systolic daytime blood pressure

- To assess the efficacy of B244 versus vehicle in reducing mean ambulatory diastolic daytime blood pressure
- To assess the efficacy of B244 versus vehicle in reducing mean ambulatory nightime blood pressure
- To assess the efficacy of B244 versus vehicle in reducing mean 24 hr blood pressure

4.3 Exploratory Objectives

- To evaluate if B244 administration on the skin twice daily for 28 days will affect the levels of inflammatory biomarkers. To explore microbial content, microbiota composition, and B244 presence/absence at baseline and Day 28.
- To evaluate the difference between daytime and nighttime ambulatory blood pressure
- To explore and compare the blood pressure change in different ethnic groups, including African American, Caucasian, Asian and Hispanic.

5 ENDPOINTS

5.1 Safety & tolerability:

- Safety and tolerability endpoints will consist of all adverse events reporting during the study duration.

5.2 Efficacy:

- Difference in mean in clinic systolic BP between the active and vehicle groups
- Difference in mean in clinic diastolic BP between the active and vehicle groups.
- Difference in mean ambulatory systolic and diastolic daytime blood pressure

5.3 Exploratory:

- Difference in inflammatory biomarkers between active and vehicle groups
- Microbial content, microbiota composition, and B244 presence/absence at baseline and Day 28.

6 STUDY DESIGN

- This is a Prospective, Vehicle Controlled, Double Blinded, Multicenter, Randomized, 2 arm, Phase II trial, comparing the effect of twice daily application for 4 weeks of B244 vs. vehicle on BP.
- We will enroll up to 116 patients and complete 104 patients
- Mean daytime ambulatory blood pressure is defined as BP obtained between 8am - 4 pm

- Mean nighttime ambulatory blood pressure is defined as BP obtained between 10pm - 6am
- After screening and recruitment, participants will be randomized to active or vehicle B244 application for 28 days. Subjects will apply IP twice-a-day as follows:
    - 4 pumps to the face
    - 4 pumps to the face and 4 pumps to the torso
- Subjects will be provided with microbiome friendly shampoo and cleanser to use for the duration of the study
- Randomization will be 1:1 into Group 1 (4 pumps) or Group 2 (8 pumps) so that equal number of patients will be treated in each Group of the study.
- All B244 randomized subjects will be treated at the dose of $8x10^9$ cfu/ml
- Screening will occur at Study Week -2 (Days -14 to -7)
- Randomization will occur during the baseline period for the study
- Clinical assessments of response to treatment will be made at Study Days 1 (baseline); Study Days 7, 14, 21, 28 and 42.
- Safety evaluations will consist of review of participant's medical history at screening and on-going assessment of adverse events reported throughout the study duration.

7 SELECTION OF STUDY PARTICIPANTS

7.1 Number of Participants Planned

It is estimated that approximately 116 participants will be consented in order to provide 104 completed participants for randomization, treatment, and inclusion in the primary analysis.

7.2 Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Participants eligible for enrollment in the study must meet all the following criteria:

- Male and female subjects ≥18 years of age
- In good general health as determined by a thorough medical history and physical examination, and vital signs
- Clinical diagnosis of elevated Blood Pressure defined as:
    - Having systolic prehypertension measurements having systolic BP (mmHg) of 120-139 and Diastolic BP (mmHg) of ≤90
    - OR
    - Having systolic Stage 1 hypertension measurements having systolic BP (mmHg) of 140-159 and Diastolic BP (mmHg) of ≤100

- Hypertension treatment naïve patients, defined as those patients who have never been treated with antihypertensive medications or have been off any hypertensive treatment for a period of 12 weeks or longer.
- Willing to refrain from using any antihypertensive treatments, other than the investigational product, including herbal supplements, systemic use of steroids, chronic use of NSAIDS, any antihypertensive agents, such as beta-blockers, diuretics, ACE inhibitors, CA channel blockers, Alpha blockers, Central Acting agents and vasodilators.
- Ability to comprehend and comply with procedures
- Agree to commit to participate in the current protocol
- Provide written informed consent prior to any study procedure being performed (all subjects should be able to understand the informed consent form and any other documents that subjects are required to read)

7.3 Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Participants will be excluded from the study if any of the following criteria are met:

- Pregnant and/or lactating women
- Patients on treatment for Benign Prostatic Hyperplasia (BPH)
- Clinically significant history of cardiovascular disease (i. e. PCI, CABG MI (if event occurred $\leq$ 12 months), atrial fibrillation, frequent PAC, cardiac rhythm disorder, syncope, valve repair/replacement, heart transplantation, PTA, peripheral bypass surgery, endarterectomy, unstable angina, TIA, stroke and NYHF category II, II and IV heart failure.
- Patients with renal failure, significant kidney or renal disease defined as having creatinine level of $\geq$ 1.4 mg/dL
- Presence of any condition (medical, psychological, social, or geographical), actual or anticipated, that the Investigator feels would restrict or limit the patient's successful participation for the duration of the study
- History of migraines and/or anxiety, where patient is unable to refrain from the use of beta blockers
- History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
- The participant has been previously randomized in this study
- Subjects with clinical diagnosis of Type I Diabetes
- Subjects with arm circumference of $\geq$42 cm
- Any condition that would prevent the subject from participating in the trial in the opinion of the evaluation physician

- The participant has received an investigational product within 30 days prior to randomization
- Prior use of any product containing B244 or Nitrosomonas eutropha
- Unable to lie flat or sit for 15 minutes
- Concurrent participation in other trials

8 PARTICIPANT ENROLMENT

8.1 Consenting Participants

Informed consent for participation in the study must be obtained before performing any study-specific procedures.

Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site in secure study files. Consent will be obtained by trained research study staff trained in taking informed consent. The study will be explained with the opportunity for the participant to ask questions. If a participant wishes to enter the study, a consent form will be completed and signed.

8.2 Screening for Eligibility

After informed consent has been obtained, to determine participant eligibility for enrollment in the study, screening assessments will be performed within 2 weeks (-14 days to 0) prior to the Baseline visit and first dose of the investigational product (IP) and confirmed at randomization. All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before randomization on Day 1. The participant's medical history and medication use will be reviewed. A complete physical examination including height, weight and vital signs will be performed.

All screening assessments are listed in the Time and Events Table (Appendix A). A participant must meet all inclusion criteria, and none of the exclusion criteria, to be enrolled and randomized in this study. The Investigator and team will maintain a screening log to record details of all persons screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.3 Study Withdrawal and Withdrawal From Investigational Product and Stopping Criteria

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator.
Reasons for withdrawal (participants who refuse to complete any remaining study visits) or discontinuation (participants who prematurely stop the application) at any time during the study may include, but are not limited, to the following:

- For safety reasons, either at the discretion of the Investigator or at the participant's request
- For protocol violations at the discretion of AOBiome
- Due to concomitant therapy that could interfere with the results of the study (the Investigator will report all such information on the CRFs and decide, in accordance with AOBiome, whether the participant is to be withdrawn).

The reason for participant study withdrawal will be recorded in the electronic Case Report Form (eCRF). Data from participants withdrawing from the study will be considered evaluable up to the point at which they are withdrawn using the same criteria for evaluability as for participants who complete the study.

8.4 Screen Failures

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to AOBiome.

8.5 Early Termination

Participants who have discontinued the study early will be evaluated by the Investigator at the Unscheduled Visit. See the list of assessments to be performed at the Unscheduled Visit in the Time and Events Table (Appendix A). Participants with ongoing AEs or SAEs believed to be possibly related to investigational product (IP) will continue to be followed until resolution or for 30 days as warranted by the nature of the AE.

9 STUDY TREATMENT

9.1 Investigational Product

Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from the Sponsor upon request.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the IP will be limited to the Investigator and authorized site staff. Investigational product must be dispensed or administered only to participants enrolled in the study and in accordance with the protocol.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance. The Investigator or designated site personnel must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to the sponsor and the amount administered to participants. The required accountability unit for this study will be the bottle. Discrepancies are to be reconciled or resolved.

Product name:	B244, 30ml/bottle	Vehicle, 30ml/bottle
Dosage form:	B244 suspension	Vehicle solution
Unit dose strength:	$8x10^9$ cfu/ml	50nM Na_2HPO_4-2mM $MgCl_2$ (pH 7.6)
Route/administration/duration:	Topical application BID for 4 weeks	Topical application BID for 4 weeks
Dosing instruction:	Face: 4 pumps total of spray to saturate the entire face. Face and Torso: 8 pumps total - 4 pumps of spray to saturate the entire face and 4 pumps to the torso Applications should occur in the morning and at night for 4 weeks.	Face: 4 pumps total of spray to saturate the entire face. Face and Torso: 8 pumps total - 4 pumps of spray to saturate the entire face and 4 pumps to the torso Applications should occur in the morning and at night for 4 weeks.
Physical description:	Odorless, cloudy, light pink suspension	Odorless, clear, and colorless suspension
Manufacturer/source of procurement:	AOBiome, LLC	AOBiome, LLC

The contents of the label will be in accordance with all applicable regulatory requirements. B244 and matching vehicle will be packaged in identical 30 ml white metered bottles.

9.2 Dose Changes

No dose changes are anticipated.

9.3 Storage conditions

All investigational drug supplies in the study will be stored in a secure, refrigerated (2-8OC) safe place, under the responsibility of the Investigator or other authorized individual.

9.4 Description of Blinding Method

This study will be double-blinded: neither Investigator(s), nor study participants, nor those involved in the conduct of the trial (including sponsor staff) will be aware of the treatment the participants are receiving.

9.5 Treatment Assignments:

This is a double blind study. Participants will be assigned to study treatment in accordance with the randomization schedule generated for the allocation of vehicle or B244 prior to the initiation

of the trial. Randomization will be centrally-based and performed using an appropriate IWRS (an automated randomization system).
Each participant scheduled to receive investigational product (IP) will receive a randomization number at the time of randomization. The randomization number will be used to identify the study medication kit assigned to the participant and indicate the treatment to be administered to that participant.

9.6 Treatment Compliance

Study treatment must be dispensed or administered according to procedures described herein. Only participants enrolled in the study may receive study treatment. Only authorized site personnel may supply study treatment. Participants will record use of the study medication utilizing the study diary at the time of use each day. Participants will review study medication compliance with the Investigator or designee. Any missed doses, timing, and reason for missed dose will be recorded in the eCRF. There should be no doubling of doses to make up for missed doses. If a dose is missed, the next dose of study medication should be taken as scheduled.

Study staff will weigh the IP at the beginning of every visit. Weight will be recorded in the eCRF.

9.7 Treatment Application

Subjects will receive a kit consisting of three 30 ml bottles at the Baseline visit for application. Subjects will be instructed in the use of the spray bottle and asked to self-administer the Investigational Product as follows:

- Face: 4 pumps of Investigational Product must be applied twice-a-day to the entire face for 28 days. Subject should saturate the application area well.
- Face and torso: 4 pumps of Investigational Product must be applied twice-a-day to the entire face and 4 pumps of drug must be applied to the torso for 28 days. Subject should saturate the application area well.
- Subjects may not wash the application site after applying the IP
- Subjects will be asked to let the product air dry.
- The spray bottles must be stored in the refrigerator. DO NOT FREEZE.

9.8 Treatment of Investigational Product Overdose

The sponsor does not recommend specific treatment for an overdose. Washing with conventional soap and water will remove the product. The Investigator will use clinical judgment to treat any overdose.

9.9 Product Accountability

In accordance with federal and local regulatory requirements, the Investigator and designated site personnel must document the amount of investigational product dispensed to study participants, the amount returned by study participants, and amount received and returned to the sponsor, when applicable. Product accountability records must be maintained throughout the course of the trial. Any quality issue noticed with the receipt or use of an IP (deficient IP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly reported to the Sponsor, who will initiate a complaint procedure.
All investigational product must be stored in a secure locked room with access limited to the Investigator and designated site personnel. Study product is to be stored in a refrigerator between 2-8 degrees C. Maintenance of a temperature log is required.
Under no circumstances will the Investigator allow IP to be used other than as directed by this Clinical Trial Protocol, or dispose of IP in any other manner.

9.10 Unblinding Procedures

The Investigator may unblind a participant's treatment assignment only in the case of emergency or in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant, as determined by the Investigator. It is preferred (but not required) that the Investigator first contacts the medical monitor to discuss options before unblinding the participant's treatment assignment. The Investigator must notify the Sponsor as soon as possible when a participant's treatment assignment is unblinded without revealing the treatment assignment of the unblinded participant unless that information is deemed important for the safety of participants currently in the study. The date and reason for the unblinding must be documented in the participant's study record. The Medical Monitor may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to clinical Investigators in accordance with local regulations and/or sponsor policy.

9.11 Retrieval and Destruction of Investigational Product

All partially used or unused treatments will be returned to the site as brought by study participants. A detailed treatment log of the returned IP shall be established.

The site will not destroy unused IP unless the Sponsor provides written authorization to the contrary.

9.12 Permitted Medications

All participants will be screened for concomitant medications prior to inclusion into the study. Any concomitant medication to treat adverse events will be recorded in the Concomitant Medication section of the eCRF.

9.13 Prohibited Medications

Participants will be prohibited from taking any antihypertensive medications including herbal supplements, any antihypertensive agents, such as beta-blockers, diuretics, ACE inhibitors, CA channel blockers, Alpha blockers, Central Acting agents, vasodilators. Chronic use of NSAIDs and steroids will also be prohibited.

9.14 Lifestyle Restrictions

9.14.1 Use of Shampoo and Soap during the trial

At the beginning of the trial, subjects will be provided Mother Dirt biome friendly shampoo and cleanser to use for the duration of the trial. Unlike conventional cleansers, Mother Dirt Shampoo and cleanser do not contain preservatives that harm Ammonia Oxidizing Bacteria.

They have been formulated not to harm the ingredients that are present in the IP.

Although study soap and shampoo is provided, subjects will be asked to refrain from washing the treatment areas with shampoo and/or study soap starting from Baseline through Day 28. Subjects may use soap and shampoo to wash other part of their body not treated during the study. At Day 28 (end of study drug application) subjects will be asked to go back to their regular regimen and use preferred shampoo and soap.

Subjects may not wash their face with soap and water AFTER each application.

9.14.2 Use of makeup

- Subjects will be asked to wear no makeup or minimal makeup (if needed) for the duration of the study. Use of anti-aging, anti-acne, moisturizing, and sunscreen products on the face will be prohibited during the study.
- Subjects must avoid prolonged periods of sun exposure and use of tanning beds during the study. Extra care should be taken to wear protective clothing, including sunglasses, and avoid sun exposure from 10 AM to 2 PM.

9.15 Handling of Investigational Product

Subjects will receive a kit containing three 30 ml white bottles. Each bottle will be used for 10 days and brought to the weekly study appointment. Subjects will be asked to refrigerate bottles that are not in use. The bottle which is being used for treatment at a given week may be placed on the counter to be used during the treatment period.

Subjects will be asked not to subject the treatment kit to conditions which are unnatural or harmful to the product, such as excessive heat (temperatures over 77°F (25°C) and freezing temperatures (at 0^{o}C). Subjects may travel with their study medication but should not leave it in

the hot car, outside in the cold temperatures etc. Subjects will also be asked not to tamper or cause damage to IP.

9.16 Treatment compliance

Each site participating in the trial will be instructed to assess subject's compliance by weighing the investigational product pre and post application (after one week of use). Sites will be provided scales, which will be calibrated prior to each use. Study personnel will be instructed to record measurements into the eCRF.

10 CONTRACEPTION REQUIREMENTS

Effective contraception is required for all women physiologically capable of becoming pregnant during study participation. Women of child-bearing potential must agree to use an acceptable form of contraception for up to 2 weeks after the study completion as detailed. Women of childbearing potential are defined as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the study participant). Periodic abstinence (i.e., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an IUD or IUS or other forms of hormonal contraception that have comparable efficacy, for example hormone vaginal ring or transdermal hormone contraception.
- Use of barrier methods (i.e., condom, diaphragm) used with a spermicide (i.e., foam, cream, or gel that kills sperm)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 90 days before the baseline visit.
Male participants of the study who are having sexual intercourse with a woman who can become pregnant must use an acceptable form of birth control while participating in the study. Additionally, male participants are expected to let their female partners know of their participation in a research study of a drug, and that the effects of the drug on an unborn baby and on a pregnant woman are unknown. Male participants will also be expected to provide their female partners with the contraception requirements information previously described and the study doctor's contact information for questions.

Payment for all aspects of obstetrical care, child-or related care will be the study participant's responsibility.

In case of pregnancy, Investigational Product should be discontinued and the Sponsor should be informed immediately. Follow-up of the pregnancy will be mandatory until the outcome is available.

11 STUDY PROCEDURES

11.1 Pre-screening procedures

Study subjects will be recruited from among participating hospitals, clinics, and diagnostic centers, under the responsibility of a participating Investigator. Prior to initiation of the recruitment phase, participating Investigators will identify a pool of potential study subjects. Each of these centers will identify potentially eligible patients in advance, by either reviewing past medical records and diagnoses, screening in clinics, referral from other physicians, or other sources of recruitment, to identify those aged 18 or older with clinical diagnosis of pre and Stage I hypertension.

11.2 Informed Consent Procedures

Eligible participants may only be included in the study after providing a consent using the IRB-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the participant's source documents. The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

11.3 Study Assessments

Study activities will take place according to the Time and Events table (Appendix A).

11.4 Inclusion procedures

Once all inclusion/exclusion criteria are fulfilled, the patient becomes eligible for randomization and inclusion into the treatment period. Treatment allocation will be performed as stated above in Section 9.5. Study medication will be delivered as stated in Section 9.7. Patients will be counseled on product application and diary completion.

11.5 Timing of patient's visits to the clinic

Patients will be asked to report to the clinic for their weekly appointments between 6am-10 am due to the fact that that systolic and diastolic blood pressures display a circadian rhythm in most individuals. If a subject is unable to schedule an appointment within this time frame, study staff

will be asked to reschedule the patient to a day when they are able to come in within predetermined time frame.

11.6 Description by type of visit

11.6.1 Screening Visit (-14 to -7)

This visit should occur between the hours of 8am +/- 2 hrs

- informed consent completed and signed
- inclusion and exclusion criteria
- demographic data
- medical/surgical history
- current medications
- smoking status
- physical exam
- body weight
- height measurement
- obtain in clinic blood pressure and heart rate
- 12-lead ECG
- blood for clinical chemistry
- urine pregnancy test (for women of childbearing potential)

11.6.2 Study Day-1A (-7 to 0)

This visit should occur between the hours of 8am +/- 2 hrs

- obtain in clinic blood pressure and heart rate
- provide 24 hr ABPM device to the patient
- train the patient on the use of the machine and provide instructions

11.6.3 Study Day 1B-Baseline visit

This visit should occur between the hours of 8am +/- 2 hrs

- Remove ABPM machine and check on the readings to make sure equipment performed as expected.
- blood for biomarkers
- allocation of a randomized treatment kit number via IWRS
- delivery of the corresponding pack of Investigational Product
- obtain skin swab samples pre drug application
- Study counseling
- Provide subjects with study soap and shampoo

- Study diary
- first application of Investigational Product (under medical supervision)
- obtain study medication weight for Investigational Product compliance
- start AE monitoring

11.6.4 Study Visit 1R-Repeat ABPM

If the ABPM technical acceptance criteria are not met during the Study Day 1B reading, the ABPM session may be repeated. In the event of technical failure, study coordinators will not perform any study related activities outlined in visit 1B prior to repeating the ABPM session.

Repeat monitoring may be scheduled up to 48 hours after the failed monitoring.

This visit should occur between the hours of 8am +/- 2 hrs

- provide 24 hr ABPM device to the patient
- train the patient on the use of the machine and provide instruction

The patient will come back on Day 2 to remove ABPM machine and check on the readings to make sure the equipment performed as expected.
If the machine performed as expected, then Study Day 1B activities will be performed as outlined in the section above.

11.6.5 Week 1, 2, 3 (Day 7, 14, 21) study visit

This visit should occur between the hours of 8am +/- 2 hrs

- recording of AEs if any
- concomitant medications
- weight
- obtain in clinic heart rate and blood pressure
- obtain study medication weight for Investigational Product compliance
- blood for biomarkers(Day 14 only)
- check study diary
- study counseling
- provide subjects with study soap and shampoo (when necessary only)

11.6.6 Week 4-A visit (Day 28)

This visit should occur between the hours of 8am +/- 2 hrs

- recording of AEs if any
- concomitant medications
- weight
- obtain in clinic heart rate and blood pressure
- check of Investigational Product compliance
- 12-lead ECG

- blood for biomarkers
- Blood for HbA1C
- check study diary
- study counseling
- Skin swab samples
- Provide patient with a 24 hrs ABPM machine
- Subjects should return all bottles of their Investigational product at this visit
- Subjects should return unused soap and shampoo that were provided by the sponsor

11.6.7 Week 4-B visit (Day 29)

- Remove ABPM machine and check on the readings to make sure equipment performed as expected.

11.6.8 Study Visit 4R-Repeat ABPM

If the ABPM technical acceptance criteria are not met during the Study Day 4B reading, the ABPM session may be repeated.

Repeat monitoring may be scheduled up to 48 hours after the failed monitoring.

This visit should occur between the hours of 8am +/- 2 hrs

- provide 24 hr ABPM device to the patient
- train the patient on the use of the machine and provide instruction

The patient will come back on Day 2 to remove ABPM machine and check on the readings to make sure the equipment performed as expected.

11.6.9 Week 6 final visit (Day 42)

This visit should occur between the hours of 8am +/- 2 hrs

- recording of AEs if any
- obtain in clinic heart rate and blood pressure
- record concomitant medications
- weight
- skin swab samples

11.6.10 Unscheduled/Unanticipated Study visit

Every attempt should be made to complete the follow-up visits during the defined window periods. In the event the subject is unable to come in for the follow-up visit or if an event arises that requires patient to come in to the research center, subjects should be scheduled for the Unscheduled visit.

During the visit, the following will be obtained:

- recording of AEs if any
- obtain heart rate and blood pressure
- record concomitant medications
-
- obtain study medication weight for Investigational Product compliance
- 12-lead ECG
- whole blood and serum for biomarkers
- physical exam
- study diary
- skin swab samples

12 METHODS OF ASSESSMENTS

12.1 Skin Swab Samples

Skin swab samples will be collected as Described in Appendix A, sampling the treatment areas at Baseline, Day 28 and 42. . Study staff will perform swabbing procedures during subject's visit. Swab samples will need to be stored in the -80 freezer until the end of the study, when samples will be shipped to the Sponsor.

Swab samples may be subjected to DNA sequencing. Samples will be used for study of the skin microbial diversity and microbiome analysis While this is not our intention to study participants genome, participants sequence may be included as part of this analysis. Samples may be stored in the freezer until future research. We will keep the specimen for up to 5 years, or until analyzed. If we complete our research and no longer need to keep the specimens, we will destroy them. Specimens will be coded and no identifiable participant information will be used. Results will not be returned to the subjects or the investigators

12.2 Blood Pressure Measurement

Blood pressure readings will be obtained at every visit as described in Appendix A (schedule of events). Subject should be asked to remove all clothing that covers the location of cuff placement. The individual should be comfortably seated in the chair, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum). Neither the patient nor the observer should talk during the measurement. After 5 minutes sitting, serial clinic BP measurements and heart (x3) rate will be performed, using the non-dominant arm with a calibrated electronic sphygmomanometer. The average of the second and third readings will be documented.

12.3 ABPM Measurements

12.3.1 ABPM monitoring schedule

ABPM will occur twice during the study. Subjects should report to the office at 8 AM + 120 minutes such that they are hooked up and dosed as close to 8:00 A.M. as possible (window 6:00 AM – 10:00 AM).

12.3.2 Office visit

Subjects must arrive at the office for ABPM hookup NOT HAVING TAKEN that day's dose of study medication, and at an appropriate time so that ABPM hookup, dosing of study medication, and start of the ABPM test is at 8 AM + 120 minutes (window 6:00 AM – 10:00 AM). Subjects who are non-compliant will be rescheduled for the following day.

12.3.3 ABPM test

The ABPM device will be placed on subject's arm during the clinic visit and recording device will obtain 24-hour blood pressure and heart rate measurements. The ABPM device and cuff may only be removed at the office, after a final manual reading is performed using the ABPM device. The ABPM device will be automatically programmed to inflate every 20 minutes throughout the recording period. The duration of the ABPM test is 24 hrs.

ABPM data will then be transmitted via modem to the Core Lab. Based on pre-established criteria, the ABPM will be reviewed by the Core Lab to determine if it was a technically successful monitoring. If technically unsuccessful, the monitoring may be repeated.

12.3.4 ABPM technical success/failure criteria

The following are the technical acceptance criteria against which subject ABPM data will be evaluated:

- Subject dosing of study medication must occur no earlier than 6:00 AM and no later than 10:00 AM.
- There should be at least one (1) manually initiated ABPM reading after dosing of study medication. If no manual post-dose reading was recorded, START TEST time will equal the 1st valid reading after dosing, provided that the reading occurs between 6:00 AM and 10:00 AM.
- There should be a final manual reading on or after 24 hours of recording. If a manual reading was not recorded, the first recording after 24 hours will be considered the last valid recording of the session.
- There must be at least one (1) valid reading per hour with the following possible exception: no more than three (3) non-consecutive hours with zero (0) valid readings during the recording period and two (2) consecutive hours with zero (0) valid readings during the recording period.

Failure to achieve any one of the above criteria will result in the ABPM being declared a technical failure.

If a subject has a technical failure on their repeat recording at Baseline, those subjects will be excluded from the study. However, if subjects passes their baseline and fails the final repeat recording , data will be included in the Office BP analysis but be excluded from the ABPM analysis. We would estimate that this will occur in less than 5% of patients.

12.3.5 Repeat ABPM

If the ABPM technical acceptance criteria are not met the ABPM session may be repeated. Repeat monitoring may be scheduled up to 48 hours after the failed monitoring.

12.4 12-lead Electrocardiograms

Standard safety 12-lead ECGs will be performed at Screening and Week 4.
Standard 12-lead ECGs will be performed according to the site SOPs. ECGs should be performed after the subject has been resting supine for ≥ 5 minutes. The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be collected: PR interval, QRS interval, QT interval, and QTc interval (QTcB; Bazett‟s correction). All ECGs must be evaluated by a qualified physician for the presence of abnormalities.

If clinically significant abnormalities are found, the study subject will NOT be allowed into the study.

12.5 Physical Examinations

The physical examination will be performed at Screening and at Unticipated visit should one occur. The physical examination includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic systems).

12.6 Laboratory Assessments

Blood samples should be taken using standard venipuncture techniques. Blood sampling will be performed according to the site SOPs.
The following laboratory variables will be determined as outlined below:

The following routine clinical chemistry test will be performed at Screening: Fasting glucose, Uric acid, BUN (blood urea nitrogen), Creatinine, BUN/creatinine ratio, eGFR (estimated glomerular filtration rate), Sodium, Potassium, Chloride, Calcium, Albumin, HbA1C, Bilirubin, Alkaline phosphatase, AST (aspartate aminotransferase), ALT (alanine transaminase), CBC.

Patients will be asked to fast before all blood tests are done.

The total blood volume collected for clinical labs for the Screening visit will be approximately 5 ml of whole blood.

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the site. The Investigator or designee will indicate whether or not the value is of clinical significance. If the result of the clinical chemistry test from the samples taken during the screening phase is indicated as clinically significant, the study subject will NOT be allowed into the study.

12.7 Biomarkers

In addition to the blood drawn for the safety laboratory assessments, additional whole blood and serum samples will be collected for the biomarker analysis Day 1B (Baseline), Day 14 and Day 28.
Samples will be processed on site and stored in the - 80° C Approximately 30 ml of whole blood will be drawn for biomarkers at each visit. Patients will be asked to fast for at least 8 hrs before blood for biomarkers is drawn.

Blood samples for Biomarkers will be taken at The following biomarkers will be evaluated:

1. Nitric Oxide metabolites and related biomarkers: nitrite, nitrate, total nitroso species, cyclic GMP
2. Panel of Redox-related Products/Messengers: sulfide, thiosulfate, sulfate; polysulfides, reduced and oxidised LMW thiols incl cysteine, HCys, GSH total antioxidant capacity (cu-based TAC), RedoxSys (electrochemical)
3. Acute phase proteins/stress markers: hsCRP, Cortisol
4. Pro-inflammatory cytokines/immune cell markers (Luminex): IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-18, IFN1, TNFN

12.8 Sample Shipment

All clinical chemistry samples are to be shipped overnight on dry ice to the central laboratory where samples will be analyzed.

All frozen serum and blood are to be shipped monthly on dry ice to the central laboratory. Shipments should be made only on Mondays and Tuesdays to ensure receipt of the specimens by Friday.

13 SAFETY ASSESSMENTS

Participants will report adverse events immediately to the Investigator and study personnel. A safety assessment will be performed at each visit. A manual or clinic BPx3 will be performed. Any patient with average systolic BP > 160 mmHg for two weeks or average systolic of > 170 mmHg at one visit should be discontinued and referred for further medical treatment. Likewise, any patient with average diastolic BP >100 for two weeks of readings or average diastolic BP > 105 mmHg reading at any one visit should be discontinued

13.1 Compliance

Participants will be asked to bring study medication with them to each scheduled visit. Study site will be provided with a scale and weight of the study medication will be obtained before the first use and at each visit.

13.2 Pregnancy Reporting

Any pregnancy will be reported by study participants during their study participation. Participants who report pregnancy or lactation during the review of inclusion/exclusion criteria prior to randomization will not be enrolled in the trial. In case of pregnancy, Investigational Product should be discontinued and the Sponsor informed. Follow-up of the pregnancy will be mandatory until the outcome is available.

13.3 Study Completion

A completed participant is one who has completed all study visits. Day 42 study visit is defined as the participant's last visit.

14 EFFICACY ASSESSMENTS

For each patient and for each treatment Period, two values of Systolic and Diastolic Blood Pressure respectively (average value on active: average value on vehicle) will be calculated and then the difference between the two will be compared so that each patient has a single treatment response.

15 STATISTICAL CONSIDERATIONS

15.1 Sample Size

A total sample size of 116 randomized subjects, stratified into 2 cohorts (4 pumps or 8 pumps of study drug) of 58 subjects each allows for a dropout rate of 10%. It is expected that each strata will have at least 52 subjects with sufficient data needed determine the effect of the investigational product on blood pressure.

With the planned number 52 subjects per arm, the study is powered 80%, to detect a treatment effect = 5.8, SD = 11 (higher SD than was observed in Phase 1b/2a) ,with alpha = 0.05.

Based on the above sample size, the study is powered 90% to detect the treatment effect of 5.8 and SD = 9, that were observed in the Phase 1b/2a study.

15.2 Populations for Analysis

ITT: includes all randomized participants.

Safety: includes all subjects who received at least 1 dose of study medication.

Per Protocol: subjects who administered at least 50 % of IP , have at least one baseline and post baseline in clinic systolic blood pressure measurement , and did not have any major protocol violations.

15.3 Data Analysis

The analyses will be conducted on all participant data when the trial ends. Data will be presented by strata treatment and overall.

Categorical variables will be summarized by frequency distributions (number and percentages of subjects) and continuous variables will be summarized by descriptive statistics (mean, standard deviation etc).
Adverse events will be summarized by treatment using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Separate tabulations will be produced for all treatment-emergent AEs (TEAEs), treatment-related AEs (those considered by the Investigator as at least possibly drug related), SAEs, discontinuations due to AEs, and AEs ≥Grade 3 severity. By-subject listings will be provided for any deaths, SAEs, and AEs leading to discontinuation.
Descriptive statistics for each sequence will be provided for clinical laboratory values (e.g., hematology, serum chemistry, and urinalysis) and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation. Abnormal clinical laboratory values will be listed.
All data will be provided in by-subject listings.

15.3.1 Disposition

A tabulation of the disposition of subjects will be presented, including the number enrolled, the number randomized, the number treated, and the reasons for study discontinuation will be reported. Summaries of the number in each analysis set will be summarized. Entry criteria and protocol deviations will be listed.

15.3.2 Demographic and Baseline

Demographic and baseline characteristic data summarization will be performed in order to descriptively assess the comparability of strata and treatments. Data to be tabulated will include age, race, ethnicity, height, weight, and BMI, as well as baseline characteristics related to medical history.

15.3.3 Safety Analyses

15.3.4 Definitions

All adverse events recorded during the study will be coded according to Medical Dictionary for Regulatory Activities.

15.3.5 Adverse Events

All adverse events (AEs) recorded during the study through the date of randomization through 28 days after the last dose of study drug will analyzed.
All AE's will be coded according to Medical Dictionary for Regulatory Activities and summarized using SOC and Preferred term.

AE's will be summarized using incidence rates. Therefore, each subject will only contribute once for a given adverse event SOC or PT.

A summary of the incidence of any adverse event, SAE, and adverse events leading to discontinuation will be presented. Summaries will display, by strata and treatment sequence, the incidence of patients with events, the frequency of patients with events within each primary system organ class and by preferred terms. For each preferred term and each system organ class a patient will be counted only once. For summaries on severe or drug-related AE, for a given patient, the highest severity or relationship for a specific preferred term will be considered.

15.3.6 Deaths and Serious Adverse Events

Serious adverse events and events leading to death will be summarized overall and by primary system organ class and preferred term.

15.3.7 Adverse Events leading to treatment discontinuation

Adverse events leading to treatment discontinuation will be summarized overall and by primary system organ class and preferred term.

15.3.8 Efficacy Analyses

To assess treatment effect, change from baseline in weekly systolic and diastolic blood pressure values will be analyzed using a mixed effect model that includes fixed effects of strata, treatmentvisit, and visit-by-treatment interaction , and a random effect of subjects. Estimates of the adjusted least-squares (LS) mean, difference in LS means, and corresponding 95% CIs will be obtained from the model. The same methodology will be used for assessments obtained using ambulatory blood pressure monitors. The influence of baseline factors , such as race, may be included in the models if sufficient data is available for secondary analyses. In addition, the average change of both systolic and diastolic blood pressure from baseline will be compared between treatment groups using analysis of covariance. Additional details on the efficacy analysis will be described in the statistical analysis plan.

15.3.9 Handling of dropouts or missing data

Missing data will not be imputed for analysis.
Subjects who dropout after enrollment but prior to randomization will be replaced.

15.4 Clinical Trial Protocol deviations

All the following deviations will be summarized on the all randomized patient population:

- Inclusion or exclusion criteria not satisfied.
- Deviations related to the Investigational Product administration
- Not permitted concomitant medications.

16 ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The Investigator and study staff are responsible for detecting and recording AEs and SAEs during scheduled safety evaluations and whenever such information is brought to their attention. This section of the protocol provides definitions and detailed procedures to be followed.

16.1 Definition of an AE

An AE is any untoward medical occurrence in a study participant which is temporally associated with the use of a medicinal product, regardless of its potential relationship to the medicinal product. An AE, therefore, can be any unfavorable or unintended sign, including an abnormal symptom, or disease (new or exacerbated), whether or not related to the investigational product (IP).
Examples of an AE include:

- Exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms of a drug interaction.
- Signs, symptoms of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).

AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., modification of participant's previous therapeutic regimen).

16.2 Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:
(a) results in death.

(b) is life-threatening.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

(c) requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out -patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Routine hospitalizations or elective surgeries are generally not regarded as SAEs.

(d) results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

(e) is a congenital anomaly/birth defect

(f) Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

16.3 Time Period, Frequency, and Method of Detecting AEs and SAEs

All AEs occurring after administration of the first dose of study medication and on or before the final assessment must be reported as AEs. All AEs must be recorded irrespective of whether they are considered drug-related.

At each assessment in the period defined above, AEs will be evaluated by the Investigator and recorded.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent assessments as necessary. If these have resolved, this should be documented. Changes in intensity or frequency of AEs should be recorded as separate events (i.e., a new record started).

The recording of AEs and SAEs are described in Section 14.4 ("Recording of AEs and SAEs").

16.4 Recording of AEs and SAEs

All clinical events, including either observed or volunteered problems, complaints or symptoms are to be recorded on the Adverse Events page(s) of the CRF. The need to capture this

information is not dependent upon whether the clinical event is associated with study treatment. Adverse clinical events resulting from concurrent illnesses or reactions to concurrent medications are also to be recorded. In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the participant's own words.
Each adverse clinical event is to be evaluated for duration, intensity, and whether the event may be associated with the investigational product (IP) or other causes. Start and stop dates, relationship to investigational product (IP), medical management, and alternative causality of event must be recorded in the Adverse Events section of the CRF. AEs believed to be possibly related to investigational product (IP) must be followed until resolution.

16.5 Evaluating AEs and SAEs

16.5.1 Severity Rating

The severity of an adverse event (AE and SAE) is to be scored according to the following scale:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or perform usual activity

An AE that is assessed as severe should not be confused with a SAE. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 14.2 "Definition of a SAE".

16.5.2 Relationship to Investigational product (IP)

SAEs will be classified as "**not related**" or "**related**" (including unknown).
For AEs, the relationship to study treatment is to be assessed according to the following definitions:

Definitely not related: The AE is definitely not related to the drug. This designation should be reserved for those events which occur prior to study treatment or for those events which cannot be even remotely related to study participation (e.g., injuries sustained in an automobile accident).

Unlikely related: There is no reasonable association between the study treatment and the suspected event and the event could have been produced by the participant 's clinical state or other modes of therapy administered to the participant.

Possibly related: The suspected adverse event may or may not follow a reasonable temporal sequence from study treatment administration but seems to be the type of reaction that cannot be dismissed as unlikely. The event could have been produced or mimicked by the participant 's clinical state or by other modes of therapy concomitantly administered to the participant.

Probably related: The suspected adverse event follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and cannot be reasonably explained by the known characteristics of the participant 's clinical state.
Definitely related: This designation should be reserved for those events which have no uncertainty in their relationship to treatment administration.

16.6 Pregnancy

Any pregnancy that occurs in a female participating in the study must be reported to the Sponsor within 3 working days of learning of the pregnancy. Follow-up must occur to determine the outcome of the pregnancy (including premature termination) and the status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs. Spontaneous abortions must be reported as an SAE.
Any SAE occurring in association with a pregnancy and considered by the Investigator as possibly related or related to the investigational product must be promptly reported to the Sponsor, even if the event occurred after the participant completed the study.
The Investigator must attempt to collect pregnancy information on any female partners of male participants who become pregnant while the male participant is enrolled in the study. Pregnancy information must be reported to the Sponsor as described above.

16.7 Prompt Reporting of SAEs to the Sponsor

In the case of a Serious Adverse Event the Investigator must immediately:

- **SEND** (within 1 working day, by fax) the signed and dated corresponding page(s) in the Case Report Form to the representative of the Monitoring Team whose name, address and fax number appear on the Clinical Trial Protocol, or to a designated Safety fax number provided by the Monitoring Team, as well as to the Central Database number;
- **ATTACH** a photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly documented on all copies of source documents provided to the Sponsor. For laboratory results, include the laboratory normal ranges;
- **Follow-up of any Serious Adverse Event** that is fatal or life threatening should be provided within one additional calendar week. The treatment code will be unblinded for reporting of Serious Adverse Events that are unexpected and reasonably associated with the use of the Investigational Product.

Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, including referral to a specialist if indicated. Notably he/she should follow up the

outcome of any adverse events (clinical signs, laboratory values or other, etc) until the return to normal or stabilization of the patient's condition;

- In the case of any serious adverse event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This implies that follow-up may continue after the patient has left the Clinical Trial and that additional investigations may be requested by the Monitoring Team;
- In case of any serious adverse event brought to the attention of the Investigator at any time after cessation of Investigational Product and considered by him/her to be caused by the Investigational Product with a reasonable possibility, this should be reported to the Monitoring Team.

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Primary Contact
AOBiome Reportable Events Hotline **24 Hour Phone: 617-475-1605** **Email: lweiss@aobiome.com** **Call medical monitor to email a scanned report**

17 ETHICAL AND REGULATORY STANDARDS

17.1 Ethical Conduct of Study

This clinical trial was designed and shall be implemented, executed, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.
The Investigator(s) should conduct the study in accordance with this protocol, the Declaration of Helsinki and ICH GCP guidelines and FDA regulations. The Investigator(s) and the Sponsor will sign the protocol and study contract, to confirm agreement. The Investigator(s) will not implement any amendment (deviation or changes of the protocol) without agreement by the Sponsor and IRB approval, except where necessary to eliminate immediate hazard(s) to study participants, or when change(s) involve only logistical or administrative aspects of the study. Records that may reveal the identities of participants must be well protected, with consideration given to confidentiality and the right to privacy of participants.

17.2 Laws and Regulations

This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the countries in which the clinical trial is performed, as well as any applicable guidelines. The trial will be registered and updated on www.clintrials.gov and on other sites, as deemed appropriate.

17.3 Informed Consent

Each participant must be provided with a statement that the investigation involves research and that the IRB has approved solicitation of participants to participate; a fair explanation of the procedures to be followed and their purposes, including identification of any procedures which are experimental; a description in lay language of any possible side effects; a description of any attendant discomforts and risks reasonably to be expected; a description of any benefits reasonably to be expected; a disclosure of any appropriate alternative procedures that might be advantageous for the participant; an offer to answer any inquiries concerning the procedures, and instruction that the person is free to withdraw consent and discontinue participation in the project or activity at any time without prejudice to the participant. Payment to research participants for taking part in the study is based on time and inconvenience. All information concerning payment, including the schedule of payments, must be set forth in the informed consent, including a disclosure that the Investigator is being paid to perform the stated research.
A participant must give consent to take part in the study. Participants below the age of majority in the municipality must give written assent to participate in this study. This consent must be dated and retained by the Principal Investigator as part of the study records. A downloadable digital copy shall be given to the person signing the form. The informed consent process must be documented in the participant's source documents.
The Investigator agrees that the Sponsor, its employees or agents will have the right from time to time during the course of this study to audit and review pertinent medical records relating to this clinical trial. A statement will be obtained from each person participating in the study permitting the release of his/her medical records as necessary for inspection by authorized personnel of the Sponsor, FDA, and the staff managing the clinical study.
The release of medical records and the review of the contents will be in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

17.4 Institutional Review Board/Independent Ethics Committee (IRB/EC)

The protocol and informed consent form and the electronic version of the consent for this study must be approved by the IRB. A copy of the Letter of Approval from the Board, which contains specific identification of the documents approved, must be received by the Sponsor prior to shipment of drug supplies to the Principal Investigator.
All changes to the protocol, as well as a change of Investigator, must also be approved by the IRB and documentation of this approval provided to the study monitor. Records of the IRB's review and approval of all documents pertaining to the study must be kept on file by the Principal Investigator and are subject to FDA inspection at any time. IRB renewal for approval is required each year. The Investigator is to AOBiome, in writing, of the approval to continue the study.

17.5 Clinical Monitoring/Record Keeping

There shall be no alterations in the protocol design without the written consent and approval of the Sponsor and the approval of the IRB, except in the case that participants are at immediate risk without immediate implementation of such alterations. In the aforementioned situation, the

site should notify the Sponsor and IRB of the deviation as soon as possible, and should seek the written consent and approval of the Sponsor and the approval of the IRB.
All results of this trial must be recorded on eCRFs. Each participant who has been randomized must have a completed eCRF. Reasons for termination must be stated in the early termination section. Study participants are not to be identified by name on eCRFs, but rather by coded identifiers and participant initials.
The study monitor will verify the accuracy of the data by reviewing pertinent source documents such as office records or hospital charts of the participants.
Study records include eCRFs, signed FDA Form 1572, original reports of test results, and digitally signed electronic informed consent forms. IRB approval letters and other documents pertaining to the conduct of the study are to be kept on file by the Investigator. If the study files are assigned to someone else or removed to another location, the Investigator is to notify the study monitor or Sponsor in writing of the change. All study records are subject to FDA inspection at any time.
All information supplied to the Investigator by the Sponsor before, during, and after the study is confidential. Such information is to be used solely in connection with the clinical study. The study protocol, IB, and any other pertinent study related materials or records provided are to be maintained in a confidential manner, reviewed carefully with attention to admonitions and returned to the Sponsor upon request. No part of these materials may be reproduced or transmitted in any form without prior written permission from the Sponsor.

18 ADMINISTRATIVE RULES

18.1 Curriculum Vitae

An updated, signed, and dated copy of the curriculum vitae limited to the experience, qualification and training for each Investigator and/or Sub-Investigator(s) will be provided to the Sponsor prior to the beginning of the Clinical Trial.

18.2 Archiving of Study Documentation

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.
It is recommended that the Investigator retain the study documents at least fifteen (15) years after the completion or discontinuation of the Clinical Trial. However, applicable regulatory requirements should be taken into account in the event that a longer period is required.
The Investigator must notify the Sponsor prior to destroying any study essential documents within the fifteen (15) year period following the Clinical Trial completion or discontinuation.
If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

18.3 Internal Safety Review Committee

An internal safety review committee will be set up to protect the ethical and safety interests of participants and to protect the scientific validity of the study. Adhoc safety interim analyses might be performed by an independent statistician if the safety review committee identifies potential safety signals during its routine blinded safety review. The details for the analysis plan

will be documented in the trial's Statistical Analysis Plan.

19 STUDY MONITORING

19.1 Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and by study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the Case Report Form [CRF], Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to Sponsor representatives. If any particular circuits have to be defined (e.g., e-CRF, Fax), particular attention should be paid to the confidentiality of the patient's data to be transferred. The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be timely appointed and listed. The Sub-Investigators will be supervised by and under the responsibility of the Investigator. The Investigator will provide them with a Clinical Trial Protocol and all necessary information.

19.2 Responsibilities of the Sponsor

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial. At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements, and any emergent problems. During these monitoring visits, the following but not exhaustive list of points will be scrutinized with the Investigator: patient informed consent, patient recruitment and follow-up, Serious Adverse Event documentation and reporting, outcome events documentation and reporting, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

19.3 Source document requirements

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the preidentified source data directly recorded in the Case Report Form. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics

Committee (IRB/EC), and the regulatory authorities to have direct access to source data which supports the data on the Case Report Forms (e.g., patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules).

19.4 Use and completion of Case Report Forms (CRFs) and additional requests

The sponsor or CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of sponsor or CRO.

For Electronic Data Capture (EDC):
Study sites will enter data directly into an EDC system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study site. Any changes to the data entered into the EDC system will be recorded in an automated, secure audit trail and is Food and Drug Administration (FDA) Code of Federal Regulations (CFR) Title 21 Part 11 compliant.

Data entered into the eCRF will be validated as defined in the Data Validation Specifications (DVS). Validation includes, but is not limited to, validity checks (for example, missing data, range checks) and consistency checks (logical checks between variables) to ensure that study data are accurately reported. Additionally, CRO Data Management will perform aggregate data review as defined in the DVS to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and queries reviewed by CRO personnel to assure validity as compared to source records. Manual queries may also be entered into EDC by Monitoring or Data Management personnel to address identified discrepancies.

Medical conditions/procedures will be coded using MedDRA and prior and concomitant medications will be coded using WHODrug.

At the conclusion of the study, each site will be provided with their subject CRFs in Portable Document Format (PDF) for archival. The CRF PDFs will contain subject data, audit trail information, queries including responses, and comments.

20 PUBLICATIONS

All data generated from this study are the property of AOBiome LLC and shall be held in strict confidence along with all information furnished by AOBiome. Independent analyses and/or publication of these data by the Investigator or any member of his/her staff is not permitted without prior written consent of AOBiome.

Any formal presentation or publication of data from this trial will be considered as a joint publication by the Investigator(s) and appropriate Sponsor personnel. Authorship will be determined by mutual agreement. Written permission to the Investigator will be contingent on the review by the Sponsor of the methodology and statistical analysis and any publication or presentation will provide for nondisclosure of AOBiome confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties at least 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

21 PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances is an Investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.
Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

22 CLINICAL TRIAL PROTOCOL AMENDMENTS

Any protocol amendments will be added as stand-alone documents. In addition, any and all revisions dictated by the amendments will be made in the protocol. Each time a protocol is amended, a new amended version date will be added to the cover page.
The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment. The Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 13 must be followed and the Study Lead.

23 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential. The Investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor. However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/EC) is expressly permitted, the IRB/EC members having the same obligation of confidentiality. The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial. The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account.

24 PROPERTY RIGHTS

All information, documents and Investigational Product provided by the Sponsor or its designee are and remain the sole property of the Sponsor. The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights. All the results, data, documents and inventions, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor. The complete verified database will be shared with the Operations Committee, which shall have full access to all data. The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the Clinical Trial. As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

25 DATA PROTECTION

The patient's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

26 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by applicable regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. As soon as the Investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

27 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

27.1 Decided by the Sponsor in the following cases:

1. In the event the results of the Clinical Trial do not appear to be scientifically convincing to the Sponsor;
2. If the aim of the Clinical Trial has become outdated or is no longer of interest;
3. If the information on the product leads to doubt as to the benefit/risk ratio;
4. If the Investigator has received from the Sponsor all Investigational Product, means and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon;
5. In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for GCP;
6. If the total number of patients are included earlier than expected; In any case the Sponsor will notify the Investigator of its decision by written notice.

27.2 Decided by the Investigator

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing. In all cases (decided by the sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/EC) and Health Authorities should be informed.

28 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol. The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this Clinical Trial Protocol. Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the IRB/EC prior to its implementation, unless there are overriding safety reasons. In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/EC approval/favorable opinion concerning the revised Informed Consent Form prior to implementation of the change.

29 APPENDIX A-SCHEDULE OF EVENTS

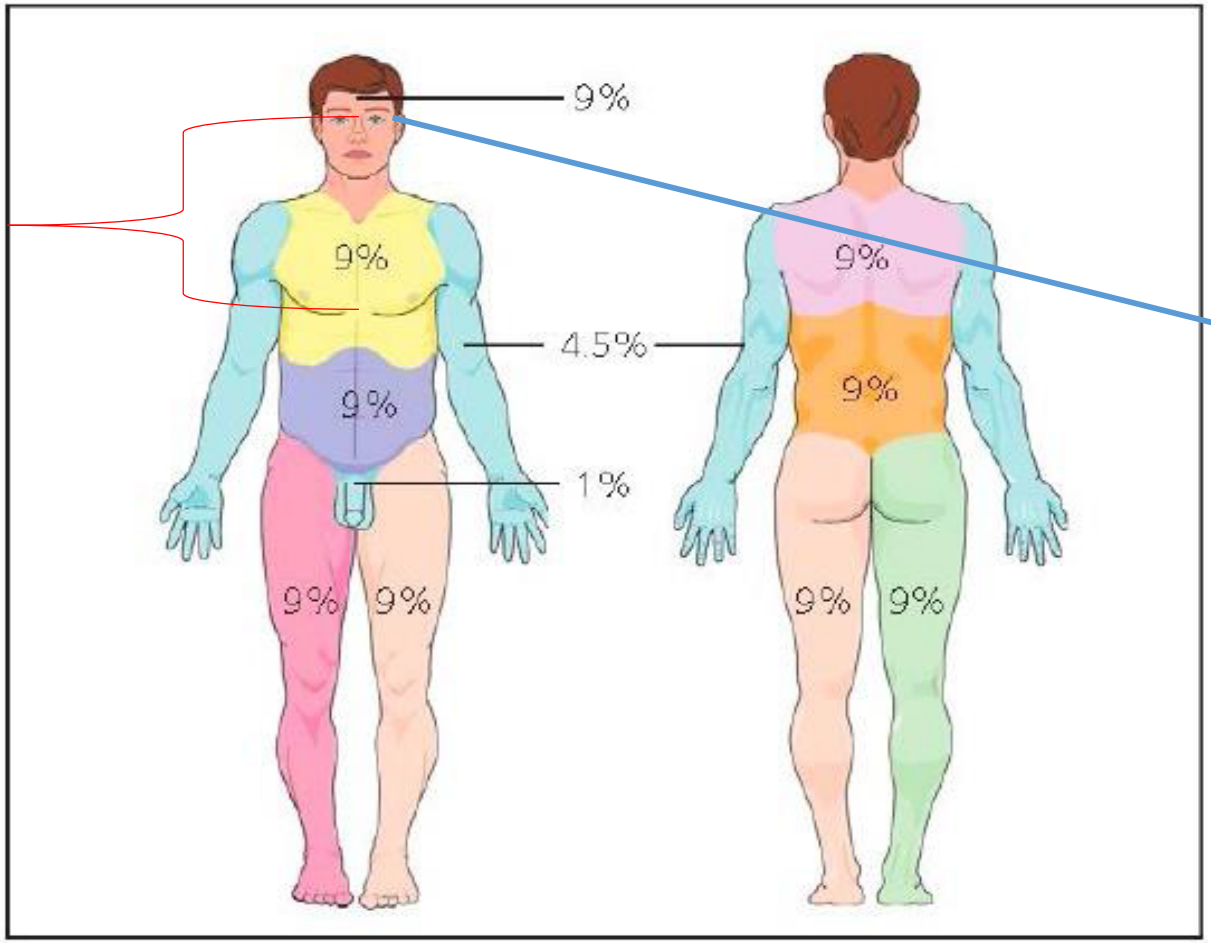
Visit Name (Da)	Screening (Day 0)	Day 1A	Day 1B	Visit 1R	Week 1 (Day 7)	Week 2 (Day 14)	Week 3 (Day 21)	Week 4A (Day 28)	Visit 4B	Visit 4R	Week 6 (Day 42)	Unscheduled Visit
Visit Window in days	**-14 to -7**	**-7 to -1**	**-1 to 0**		**+/-1**	**+/-1**	**+/-1**	**+/-1**	**+/-1**		**+/-3**	
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics	X											
Medical History	X											
Concomitant Medications	X				X	X	X	X			X	X
Smoking status	X											
Physical Exam	X											X
Body Weight	X				X	X	X	X			X	
Height	X											
12 Lead ECG	X							X				X
Clinical chemistry[8, 10]	X							X				
Blood for biomarkers[9]			X			X		X				X
In clinic BP and HR	X	X			X	X	X	X			X	X
Urine pregnancy test for WOCBP[1]	X											

ABPM placement[12]		X		X				X		X		
ABPM removal			X	X					X	X		
IWRS			X									
Dispense Investigational Product to patient			X									
Investigational Product application[7]			X		X	X	X	X				
Investigational Product compliance[6]			X		X	X	X	X				X
Counseling[4, 11]		X	X		X	X	X	X				
Soap and shampoo[2]			X		X	X	X	X[14]				
Study diary [3]			X		X	X	X	X				X
Skin swabs[5]			X					X			X	X
AEs			X		X	X	X	X			X	X

1. Urine pregnancy test for WOCBP will be done at Screening
2. Subjects are to be provided soap and shampoo at Baseline visit. However, soap and shampoo is available upon request in the event that subjects run out of their initial supplies.
3. Subjects will be asked to fill out study diary for the duration of the study (Baseline-Day 28)
4. Subjects will be counseled on the use of study medication, diary and answer any questions subject may have
5. Skin swabs will be obtained during the office visit and will be frozen in the -80 freezer and will be shipped monthly to Biostorage labs
6. Weight of an IP kit will be obtained at the at the 1B visit. Weight of an individual bottle that is currently in use will be obtained at each visit. Final weight of the kit will be obtained at Week 4A visit, when kit is returned by the patient.
7. Subjects will be asked to apply the IP twice daily as per their randomization. First IP application will happen in the office under medical supervision.
8. Patients should fast for at least 8 hours before the test. Blood for clinical chemistry will be shipped to the central lab for processing
9. Blood samples for biomarkers will be collected and processed on site. Patients should fast for at least 8 hours before the test. Samples will then be frozen onsite and shipped on monthly bases to the Central lab for storage.
10. Blood for HbA1C only will be drawn at the Week 4A visit and shipped to central lab or processing.
11. Subjects will be counseled on the use of ABPM equipment
12. If subject undergoes ABPM procedures and equipment fails, subject will be scheduled for another ABPM session within 48 hours for Visit 1R or 4R.
13. AEs will be monitored throughout the trial
14. Soap and shampoo should be returned to the study coordinator

30 APPENDIX B-BODY SURFACE AREA AND IP APPLICATION

Patients will apply 4 pumps to their face and 4 pumps to their torso (yellow surface area only)



Patients will apply 4 pumps of IP to their face

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